Osteomalacia and Renal Osteodystrophy

JACOB M. MODEST, MD; HIMESH SHETH, MD; REGINALD GOHH, MD; ROY K. AARON, MD

ABSTRACT

Osteomalacia is defined by the undermineralization of newly formed bone due to a lack of available calcium, phosphorus, or vitamin D. Causative factors of osteomalacia include nutritional deficiency, diminished absorptive capabilities (often due to gastrointestinal disorders), and renal insufficiency. Renal osteodystrophy is a specific form of metabolic bone disease defined by the presence of osteomalacia and associated hyperparathyroidism secondary to a malfunction in, or absence of, renal parenchyma. This reduces the conversion of vitamin D to its active form, thus leading to a cascade of effects that negatively impact the stability of the skeleton. Osteomalacia occurs across a spectrum of severity and can produce severe consequences for specific populations, including patients with dietary, nutritional, and absorptive deficiencies. Renal osteodystrophy affects patients with chronic kidney disease, those undergoing dialysis, and renal transplant patients. Special considerations must be taken into account when assessing the bone health of patients fitting these criteria.

KEYWORDS: Osteomalacia; renal osteodystrophy; chronic kidney disease (CKD); reduced calcium absorption

INTRODUCTION

Osteomalacia is defined as "the lack of available calcium or phosphorus (or both) for mineralization of newly formed osteoid."[1] In classic papers, Henry Mankin, former chair of orthopedics at Harvard and Massachusetts General Hospital, reviewed the osteomalacias and the identification of vitamin D deficiency as the prototype of the disease.[2-4] He provided an etiological classification of the osteomalacias as deficiency, absorptive, and renal. In addition to vitamin D deficiency, osteomalacia can be produced by a variety of other conditions that impair mineralization (**Table 1**). The most common causes of osteomalacia are gastrointestinal disorders causing malabsorption, including enteric, hepatobiliary, and pancreatic diseases, short bowel syndrome, and some bariatric procedures. Less commonly these days, but still to be considered, are medications including the anticonvulsants phenobarbital, phenytoin, and carbamazepine, which can alter hepatic vitamin D metabolism. Renal osteodystrophy is a special case in which osteomalacia coexists with hyperparathyroidism.

Table 1. Etiological Classification of Rickets and Osteomalacia

I.	**Deficiency Rickets and Osteomalacia**
	A. Vitamin D deficiency
	B. Calcium deficiency
	C. Phosphorus deficiency
	D. Chelators in diet
II.	**Absorptive Rickets and Osteomalacia**
	A. Gastric abnormalities
	B. Biliary disease
	C. Enteric absorptive defects
III.	**Renal Tubular Rickets and Osteomalacia**
	A. Proximal tubular lesions
	B. Proximal and distal tubular lesions
	C. Distal tubular lesions (renal tubular acidosis)
	1. Primary
	2. Secondary
IV.	**Renal Osteodystrophy**

CLINICAL PRESENTATION

The clinical presentation of osteomalacia is often asymptomatic but, when severe, mainly reflects symptoms of hypocalcemia, including myalgias, muscle spasms, and bone pain. More severe symptoms related to hypocalcemia include tetany and seizures; chronic vitamin D deficiency can lead to long bone and limb angular deformities.[5]

Undermineralized newly formed bone is the hallmark of both osteomalacia and rickets, the juvenile form of osteomalacia. On radiographs, bones appear osteopenic often with a ground glass appearance and indistinct trabeculae. Stress fractures with radiodense lines adjacent to regions of radiolucency may be seen on the concave sides of bones. These are termed Looser lines, also called Milkman pseudofractures, after the aptly named radiologist, Louis Milkman, who described the radiological appearance of pseudofractures in osteomalacia (**Figure 1**). Characteristic osteomalacic

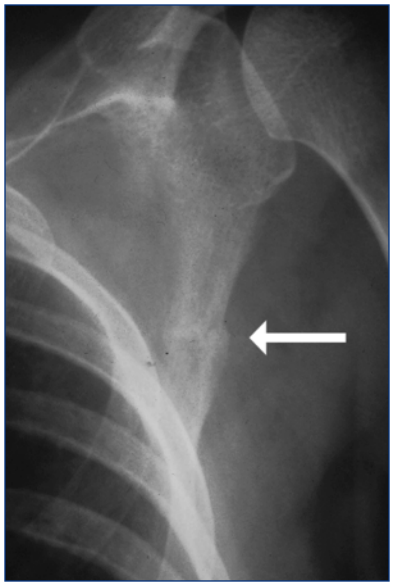

Figure 1. AP X-ray of left scapula
Looser line (Milkman pseudofracture) seen characteristically on the concave side of bone in osteomalacia (arrow).

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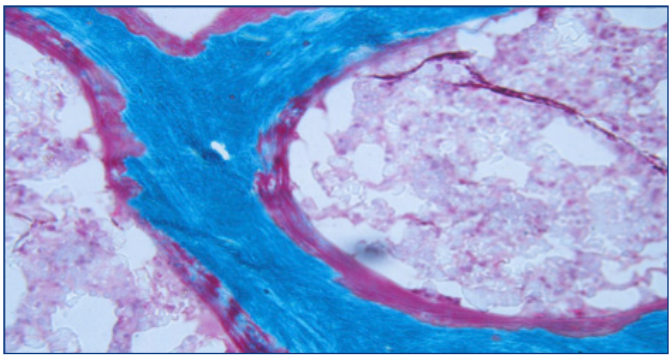
Figure 2. Histology and mineralization front in osteomalacia
Trichrome stain demonstrating unmineralized, thick osteoid borders (red) rimming the length of trabeculae.



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hip fractures resemble slipped femoral capital epiphyses and may occur over time with minimal symptoms. Stress fractures are common and may be seen by MRI and technetium bone scans; they may not be apparent radiographically until a healing callus is present. Histologic characteristics of osteomalacia are trabeculae covered with long, wide osteoid seams due to the lack of mineralization, contributing to the ground glass radiologic appearance of trabeculae (**Figure 2**). On bone biopsy with tetracycline labeling, smudged, indistinct tetracycline labels occur from the impaired mineralization.

PHYSIOLOGY OF DEFICIENCY OSTEOMALACIA

Apart from its structural function, bone serves as a reservoir for calcium.[1,4] Calcium plays a critical role in cell membrane signaling and neuromuscular signal transmission; there is a narrow range of safety for serum and cytosolic calcium concentrations. Hypercalcemia causes hypotonicity, hyporeflexia, obtundation, and coma, whereas hypocalcemia causes hypertonicity, hyperreflexia, and seizures. The homeostatic priority of maintaining soluble calcium concentration utilizes three organ systems to achieve rigorous control: the gastrointestinal, renal, and skeletal systems. The skeletal system is unique as a calcium donor because the downward pressure of transient calcium deficiency can lead to compromise of bone structure and increased fracture risk. In this context, bone resorption to maintain serum calcium homeostasis takes priority over the structural role of bone.[6]

Serum calcium exists in ionized and protein-bound forms, with the ionized form being metabolically active and critical for cell signaling. In states of decreased serum calcium, the body's homeostatic response includes regulation via PTH and vitamin D. Vitamin D is a fat-soluble vitamin which has two main sources: ergocalciferol is a plant-derived dietary source, and cholecalciferol, which derives from 7-dehydrocholesterol. After irradiation in the skin which opens these molecules' sterol rings, two hydroxylation steps take place.[7] The first occurs in the liver to form 25(OH)D, the storage form of vitamin D, and the second in the kidney to form 1,25 di(OH)D, the metabolically active form, or 24,25 di(OH) D which is less active and less regulatory. Active vitamin D raises serum calcium concentration by increasing intestinal calcium absorption, promoting a renal phosphate diuresis, increasing renal tubular reabsorption of calcium, and increasing the transfer of calcium from bone to serum. Parathyroid hormone stimulates the production of 1,25 di(OH) D, and both hormones increase serum ionized calcium concentration.[6] Vitamin D deficiency can be nutritional and has several other etiologies. Direct sunlight is required to irradiate dietary vitamin D and open its sterol rings. Individuals with reduced sunlight exposure, such as those who live in locations farther from the equator, can have lower serum vitamin D levels.[8] Additionally, heavily pigmented skin with high levels of melanin can affect the irradiation of vitamin D. Obesity and increased age can also result in reduced production of vitamin D to its active form.

DEFICIENCY RICKETS

Rickets is the juvenile form of osteomalacia and occurs in skeletons with open growth plates.[9] Because rickets and osteomalacia are failures of mineralization, it is not surprising that rickets is manifest largely in the physis (**Figure 3**). Deficiency in mineralization of the physis results in the growth of unmineralized cartilage reflected radiographically as cupping, widening, or flaring of the growth plate, with blurring of the mineralization front. Femoral neck fractures are characteristic of osteomalacia and resemble slipped capital femoral epiphyses. The prototype of the juvenile form is nutritional rickets, usually due to vitamin D or calcium

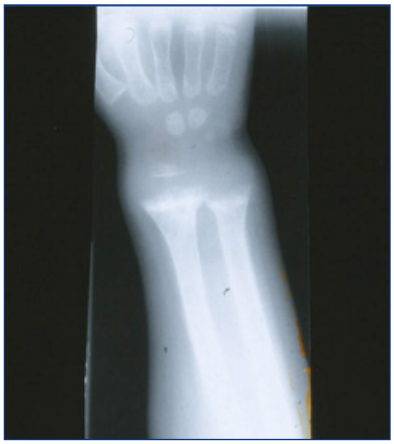

Figure 3. Epiphyseal plate in rickets
Radiograph of rachitic epiphyseal plate in the distal radius exhibiting cupping, flaring, and metaphyseal widening associated with deficient mineralization.

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deficiency. While rickets is less prevalent in the industrialized world, it is still present there in unusual situations. Rickets can be seen as a result of malnutrition in nutritionally deprived populations or as a result of individual dietary eccentricities and emotional eating disorders. Whether or not florid growth plate abnormalities are present, an index of suspicion should be maintained in children with the appropriate medical histories and atypical fractures. Bone density determination will assist in the diagnosis and detailed laboratory investigation is usually warranted.

ABSORPTIVE OSTEOMALACIA

A range of gastrointestinal conditions can cause malabsorption of nutrients and absorptive osteomalacia, decreased bone density, and fractures. Malabsorption of nutrients from the gastrointestinal tract has profound effects on the skeleton by depriving osteocytes of hormonal control and osteoid of its constituent calcium.[4] The subject of malabsorption is quite complex and, for our purposes, will be broadly considered in two forms.

(1) Pancreatic insufficiency, pancreatitis, cystic fibrosis, and hepatobiliary diseases, including cirrhosis and alcoholism, reduce the secretion of bile and pancreatic enzymes and impair the ability to digest and absorb fats including the fat-soluble vitamins, A, D, E, and K, contributing to an absorptive vitamin D-deficient osteomalacia and low serum 25(OH) D.

(2) Enteric malabsorption is due to the loss of absorptive surfaces of the duodenum and proximal jejunum. Loss of absorptive villi can be due to inflammatory diseases such as Crohn's disease, celiac disease, and sprue, surgical short bowel syndrome, or small intestinal bacterial overgrowth syndrome.

Other forms of absorptive osteomalacia occur due to intestinal binding of calcium. Calcium absorption from the gastrointestinal tract is regulated by vitamin D and PTH. Vitamin D is fat-soluble and is dependent on bile salts for absorption, which primarily takes place in the proximal duodenum and proximal jejunum. Chelating agents such as oxalate (in spinach), phytate (in coarse cereals), or excessive concentrations of phosphate or free fatty acids make calcium more difficult to absorb as calcium can bind to these molecules creating materials that are insoluble in body fluids.[3]

MALABSORPTION AND FRACTURES AFTER BARIATRIC SURGERY

Bariatric surgery has been very helpful to patients with morbid obesity. However, like many medical interventions, it has its risks and management challenges. Bariatric surgery can have negative consequences for the skeleton, including osteomalacia and increased risk of fractures.[10,11] Current procedures involve (1) Restriction or reduction in stomach size such as gastric banding and gastric sleeve procedures, and (2) Malabsorption procedures that bypass segments of the proximal stomach and small intestine such as the Roux-en-Y gastric bypass. The influences upon the skeleton that occur after surgery are specific to the procedure type, with the most pronounced metabolic abnormalities and bone loss seen after procedures that result in the most malabsorption.[12]

Bone disease among bariatric surgery patients is influenced by pre-operative abnormalities in bone and mineral metabolism related to morbid obesity. The effects of obesity on the skeleton can be profound and often center around vitamin D deficient osteomalacia secondary to sequestration of vitamin D in adipose tissue.[13] Vitamin D deficiency is often the source of hyperparathyroidism in obese individuals.

The hip is the most consistent site for bone loss after bariatric procedures. Measurements of hip bone density show losses in the range of 6–10% 1 year after bariatric procedures, and these can be seen for 10 years after surgery. The bone loss that occurs after bariatric surgery is likely multifactorial.[14,15] Proposed mechanisms include skeletal unloading, abnormalities in calciotropic hormones, and changes in gut hormones. Increased bone resorption can be assessed by elevated levels of the blood and urine bone resorption markers, NTX and CTX. Evaluation of bone biopsies up to 4 years after bariatric procedures have shown alterations in microarchitecture including decreased cortical thickness, declining mineralization, and increases in osteoid volume consistent with hypovitaminosis D and hyperparathyroidism.

The risk of fractures, including fragility fractures, in this clinical setting is increased at the hip, spine, and wrist (**Figure 4**). Management of nutritional deficiencies after bariatric procedures can often be done using high doses of ergocalciferol. After replacement, maintenance doses of calcium (1000-1200 mg/d) and vitamin D (2000 IU/d) can be used with monitoring of serum 25(OH)D, PTH, serum and urine calcium, and DEXA bone density with adjustment of supplements as necessary. Bone densities may decline but replacement therapy can often keep the densities out of the osteoporotic range.[16]

Figure 4. Vertebral compression fractures after bariatric surgery
X-ray showing multiple compression fractures (asterisks) and kyphoplasty (arrow).

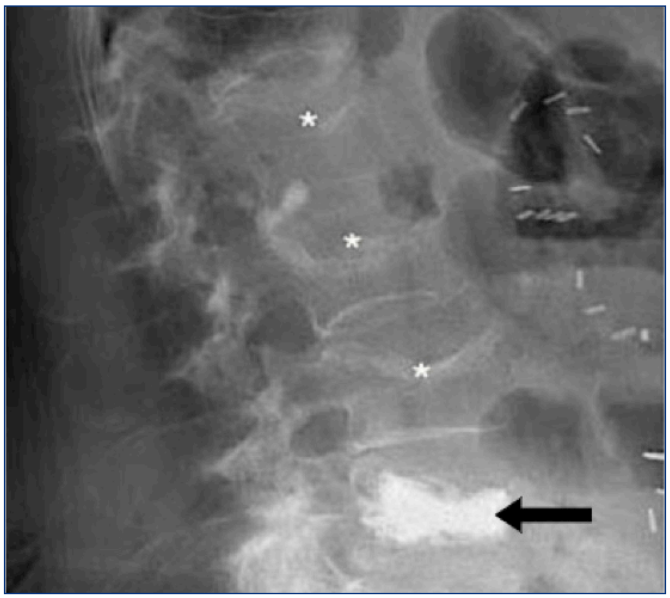
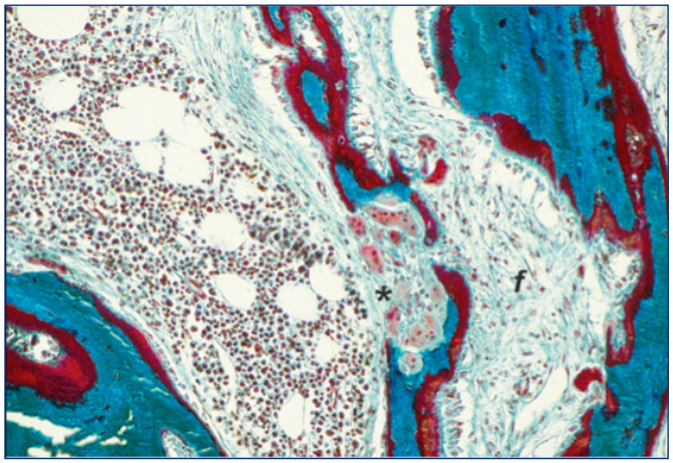


Figure 5. Histology in renal osteodystrophy
Osteitis fibrosa cystica comprised of (1) mineralization failure demonstrated by increased osteoid borders (red), (2) secondary hyperparathyroidism with osteoclastic resorption (asterisk), and (3) peritrabecular fibrosis ("f").



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RENAL OSTEODYSTROPHY

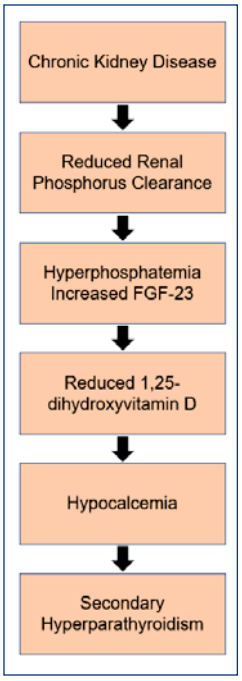
Patients with advanced kidney disease are at high risk of bone disorders that range from osteitis fibrosa to adynamic bone disease, also known as osteomalacia. Osteitis fibrosa is a result of overactivation of the parathyroid gland resulting in excess parathyroid hormone (PTH) release. This leads to increased bone turnover and, in advanced cases, brown tumor formation. Renal osteodystrophy denotes hyperparathyroidism, lack of osteoid mineralization (osteomalacia), and bone resorption, described previously as osteitis fibrosa cystica (**Figure 5**). Isolated osteomalacia is a result of over-suppression of the parathyroid gland decreasing PTH release. This results in decreased osteoclast and osteoblast activity and low bone turnover, leading to the formation of brittle bones that are prone to fractures. In addition to direct bone pathology, calcium, phosphorous, and PTH dysregulation leads to increased cardiovascular disease from vascular calcification. Hormones and minerals involved in the process include PTH, Fibroblast Growth Factor-23 (FGF-23), 1,25-dihydroxyvitamin D (calcitriol), calcium, and phosphorous (**Table 2**).

The nephron is the functional unit of the kidney, and each kidney is comprised of approximately one million nephrons. Nephrons are responsible for converting 25-hydroxy vitamin D, the inactive storage form, to 1,25-dihydroxyvitamin D (calcitriol), the metabolically active form of vitamin D. With a loss of renal parenchyma, the ability to produce active vitamin D decreases. Nephrons also regulate phosphorus homeostasis by excretion and reabsorption as needed. Nephrons are a target of FGF-23, PTH, and calcitriol. The exact mechanisms of interaction are not fully understood, but studies are ongoing. In chronic kidney disease (CKD), the number of functioning nephrons decreases over time. The physiology of CKD is summarized in Table 2. As the quantity of nephrons decreases in advanced CKD, phosphorous excretion diminishes, resulting in elevation of serum phosphorus concentration. Osteocytes sense this elevation in serum phosphorous and secrete FGF-23 which acts on the nephron and enhances phosphaturia. In addition to phosphaturia, FGF-23 also suppresses the synthesis of calcitriol. As the CKD progresses, phosphorous excretion

Table 2. Physiology & Actions of Hormones in CKD

Hormones/ Mineral	Phosphorus	FGF-23	1,25-DiOH-D (Calcitriol)	PTH
Physiology of CKD	Serum concentration increases as CKD progresses.	FGF-23 levels increase as serum phosphorus levels increase.	Calcitriol levels decrease as FGF-23 levels increase and nephron mass decreases. Calcium concentration decreases	Low serum calcium concentration and calcitriol leads to PTH secretion and increase bone resorption.
Resultant Action of Hormone	↑ FGF-23 ↑ PTH ↓ Calcitriol	↑ Phosphorous excretion in urine ↓ Serum phosphorus ↓ PTH ↓ Calcitriol	↑ Gut calcium absorption ↑ Gut phosphorus absorption	↑ Phosphorus excretion in urine ↑ Calcitriol

Figure 6. Mechanisms of CKD progression leading to secondary hyperparathyroidism.



is further impaired, FGF-23 secretion increases, and calcitriol levels decrease, ultimately resulting in hypocalcemia. These changes lead to a metabolic imbalance resulting in overactivation of the parathyroid gland and excess PTH secretion (**Figure 6**). Elevated PTH contributes to the release of calcium and phosphorous from bone, which further activates the FGF 23-vitamin D-PTH axis leading to osteitis fibrosa cystica, reduction in bone density, and resistance to fracture. Therefore, it is essential that patients with advanced CKD limit their phosphorous intake.[17] Patients on dialysis lose almost all of their ability to excrete daily phosphorous load. Even small amounts of dietary phosphorous intake will lead to significant serum accumulation.

Some degree of PTH elevation is thought to be protective of bone health by maintaining appropriate amounts of bone turnover in CKD.[18] Serum concentration above 80 pg/ml of intact PTH is diagnostic of hyperparathyroidism. Secondary hyperparathyroidism can be diagnosed if the PTH level is elevated above 80 pg/ml, advanced CKD is present, and serum calcium level is normal. Aggressive suppression of PTH to below 80 pg/ml in CKD leads to adynamic bone diseases and other adverse effects.[19] The target treatment range for elevated PTH is unclear, but expert guidelines suggest that PTH levels of 2–10 times the upper limit of normal are acceptable.[20] Progressive increase in serum PTH level, even if within the therapeutic range mentioned above, warrants intervention to prevent tertiary hyperparathyroidism. Intervention can be in the form of reducing serum phosphorus levels through dietary modification, starting patients on a phosphate binder with meals, using vitamin D analogs like paricalcitol and hectorol, or adding a calcimimetic such as cinacalcet if the PTH continues to rise. Parathyroidectomy is reserved for patients with tertiary hyperparathyroidism. Conversely, over-suppression of PTH by administering a vitamin D analog or a calcimimetic will lead to adynamic bone disease resulting in brittle bone and increased risk of fracture.

DIALYSIS

Patients on dialysis lose their ability to excrete the recommended dietary phosphate load and therefore are asked to limit phosphorous intake to less than 800 mg/day.[21] At times, this becomes challenging given the abundance of phosphorous in foods generally considered healthy, such as dairy products, beans, grains, and nuts. Phosphorous is cleared by dialysis mostly via diffusion. This clearance is limited to 800–1200 mg per dialysis session.[22,23] In our current dialysis delivery structure, patients receive dialysis three times a week. Based on this, patients are in a net positive phosphorus balance for 4 out of 7 days per week. Even with dietary phosphorus binders, it becomes challenging to regulate serum phosphorus concentration as there is active calcium and phosphorus release from bones driven by PTH secretion.[22,23] Therefore, an aggressive dietary phosphorous restriction is recommended to avoid hyperphosphatemia, elevated FGF-23, decreased serum calcium concentration, elevated PTH secretion, and increased bone resorption.

TRANSPLANTATION

Kidney transplant recipients may also experience calcium, phosphorus, and bone pathology due to adverse interactions among the parathyroid gland, kidney, and bone. Most transplant recipients with an adequately functioning transplanted kidney do not experience these pathologic interactions, but, depending on their transplanted kidney function, they may need to modify their dietary habits and regulate phosphorus intake. Studies have shown that hypophosphatemia leads to improved transplant graft survival and improved cardiovascular mortality.[24] This is thought to be due to enhanced phosphorus from functioning transplanted graft, leading to a reduction in FGF-23 level, which is linked to cardiovascular mortality.[24,25] Depending on the length of end-stage renal disease status, previous phosphorus control, and PTH levels, transplant patients are often at risk of tertiary hyperparathyroidism requiring parathyroidectomy. They are also at risk of severe hypocalcemia post parathyroidectomy due to hungry bone syndrome. In end-stage renal disease patients, persistently elevated PTH levels deplete bone of calcium and phosphorus stores. Once the parathyroid gland is removed, calcium and phosphorus are aggressively taken up by bone. This leads to a precipitous drop in serum calcium and phosphorus concentration risking acute arrhythmia and respiratory failure if unaddressed.

As kidney disease advances, either in the native or transplanted kidney, phosphorous excretion declines leading to hyperphosphatemia. This leads to elevation of FGF-23 and decreased calcitriol synthesis resulting in hypocalcemia. Hypocalcemia leads to increased elevation of PTH. Persistent, unregulated elevation of PTH can lead to tertiary hyperparathyroidism and osteitis fibrosa. Conversely, over-suppression of PTH via administration of calcitriol can also have negative consequences in the form of osteomalacia. Therefore, it is essential that patients regulate their phosphorus intake to prevent hyperparathyroidism and maintain good bone health.

CONCLUSIONS

Pathologically low serum vitamin D has profound effects on the skeleton including hormonal dysregulation of osteocytes and mineralization deficiency. (1) Reduced gastrointestinal calcium absorption exerts a downward pressure on serum calcium concentration that can lead to secondary hyperparathyroidism to maintain serum calcium but at the expense of bone calcium and resulting decreased bone density. (2) In all forms of osteomalacia, the structural function of the skeleton is sacrificed to maintain serum calcium concentration, resulting in loss of skeletal mass, reduced bone density, and elevated fracture risk. (3) Renal osteodystrophy consists of osteomalacia, secondary hyperparathyroidism, and bone resorption. The lack of renal parenchyma in CKD results in an inability to convert 25(OH)D to its active form and diminished phosphate excretion leading to hyperphosphatemia and hypocalcemia.

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